REMARKS

Claims 59, 60, 64, and 66-74 have been withdrawn as being directed towards non-elected subject matter. Applicants reserve the right to file divisional applications directed towards the withdrawn claims. Claims 38, 39, 42, 43, 53, 55, 61, and 63 have been amended to address the various objections of the Examiner. The amendments pertaining to the rejections based on the cited art are addressed primarily in connection with the §102 rejection citing Ramdi et al. New claims 75 and 82 formulate alternative claim language that is based on the aforementioned discussion of the Ramdi et al. reference. Claims 38-58, 61-63, 65, and 75-88 are currently under consideration.

Rejections Under 35 U.S.C. 35 U.S.C. § 112, Second Paragraph

Claims 39-44 and 63 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner states that claim 39 first recites "collagen" and "collagens" as integrin binding partners, but then recites the compound "type 1 collagen". The Examiner states that a claim may not recite a broad range or limitation ("collagen" or "collagens") together with a narrow range or limitation that falls within the broad range ("type 1 collagen"). The Examiner has also pointed out that certain terms within claim 39 are duplicated.

Applicants have amended claim 39 to delete the offending language "type 1 collagen" and duplicates of the terms collagen, factor X and laminin. Similarly, with reference to claim 63, the Examiner asserts that the recitation of the broader language progenitor/stem cells, together with the bracketed phrase reading "e.g. from bone marrow, adipose, or peripheral blood," (being the narrower statement of the range/limitation) is indefinite for the same reason. Applicants have amended claim 63 to delete the aforementioned bracketed phrase.

Rejections Under 35 U.S.C. §102

Claims 38-39 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Ramdi et al. (1993). The Examiner states that Ramdi et. al. teach an encapsulation methodology that is carried out in the presence of an integrin binding partner, specifically type I collagen, type IV collagen and fibronectin (citing to page 451, 2nd col. of Ramdi et al.). The Examiner asserts that Claim 38 read together with claim 39 or 41 recites a method

that reads on the cited encapsulation methodology of Ramdi et al. in that the method elaborated in the cited passage is also carried out in the presence of an integrin binding partner named in the rejected claims.

The amendment to claim 38 presented above, clarifies the nature of the encapsulation product of the invention and clearly distinguishes it over the prior art encapsulation products including the product described by Ramdi et al. referenced above. In particular, amended claim 38 clarifies that the encapsulation product is a suspension of prepared cells which the disclosure elaborates to be suitable for administration intravenously, injection into a tissue or by inhalation. The Examiner is referred to the first full paragraph of page 19 of the disclosure, describing the cell suspension and such modes of administration and the repeated reference in the disclosure, beginning at page 3, lines 32-33 (which contextualizes the invention) to cells that are conditioned to shed their capsule.

Thus the invention is concerned with cells are for the most part *individually encapsulated* in a manner that prepares them to shed their capsule. Within the suspension they are prepared for life outside the encapsulation medium by using integrin binding partners that transiently condition them to survive as individual cells pending and following exit from the capsule so as greatly increase the likelihood of their being engrafted into the tissues which they are intended to populate (outside the capsule). This is an important distinction relative to implanted beads that use integrin binding partners differently to permanently facilitate anchorage within the capsule for groups of 50,000 cells (Ramdi et al. page 450, column 1, Growth Assay). The distinction between cells meant to inhabit and flourish within a capsule (permanently encapsulated) and those "prepared" or "conditioned" to exit the capsule ("cocooned" temporarily) is further expressed in several passages in the disclosure, for example page 9, lines 10-12 ("..the present invention teaches the selection of a cell capsule to enhance the shedding of the encapsulation material from the encapsulated cell upon arrival at a selected tissue or organ in the recipient of the cell therapy."), page 9, lines 28-30 ("The present inventors explored the potential of the agarose micro-capsules in providing a **temporary home** [emphasis added] for individually transfected cells maintaining their viability and functionality"), page 9, lines 31-32 ("The microcapsules are both **biodegradable** [emphasis added] and biocompatible.."), page 11, lines 2-5 ("cells must **commit to a migratory phenotype to exit the capsule,** [emphasis added] this in turn ensures efficient penetration and engraftment of the organ. Thus, the enhanced retention and

engraftment of encapsulated cells represents a unique advantage of the present invention."), and page 24, lines 12-14 ("Also, the addition of Fibrinogen, it was found that a greater percentage of the cells were breaking out of the capsule and adhering to the flask.").

By contrast, Ramdi et al. relates to encapsulation products containing 5 x 10^4 cells per product, typically intended for implantation into a subject. Those authors demonstrate that these cells can grow (proliferate) and produce more proteins in the presence of collagen and fibronectin. It is important to note that over the ***several weeks of culture*** the cells remained (actually increased in number from initial 50,000) **within** the bead/capsule as the study was designed to demonstrate. Matrix production within the capsule (proteoglycan and other) is a prominent feature of Ramdi's work and is posited to likely influence cell growth and survival. Matrix production is a consequence of the use of larger capsules containing multiple cells that remain encapsulated for prolonged periods of time. Furthermore, multi-cellular alginate capsules described in Ramdi et al. are not suitable to be delivered as a suspension, especially into the vascular system since these large structures would be anticipated to result in embolization and occlusion of blood vessels.

Claims 38-39, 41, 44-52, 55-58, 63, and 65 are also rejected under 35 U.S.C. 102(b) as being anticipated by Schinstine et al. (US Patent No. 5,776,747). Schinstine et al. teach a method for the encapsulation of cells within a Bioartificial organ (BOA) using a number of different hydrogels and matrix and/or integrin binding supplements and gene transfection. Large numbers of cells (25,000/ul) are loaded into hollow fibers and it is proposed that the BOA is **implanted** into the host. Again, this teaching is very different from that of the instant invention which contemplates injection of single cells in suspension into the circulation or into tissues. Schinstine does not contemplate engraftment and incorporation of the prepared cell product into the host tissue. The hydrogel, matrix and/or integrin binding components are designed to contain the cells and prevent their outgrowth (as pointed out by the Examiner). This is clearly substantively different from single cell capsules designed to allow cell outgrowth into the surrounding tissue to promote engraftment.

Rejection Under 35 U.S.C. §103(a)

Claims 38-58, 61-63, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schinstine et al. The Examiner states that although Schinstine et al. does not specifically teach that the encapsulation product may contain one cell nor many of the

integrin binding partners asserted in the claims, it would have been obvious to the ordinary skilled artisan to modify the methods of Schinstine et al. to comprise the use of alternative integrin binding partners such as fibrinogen, Factor XIII or Factor XIIIa. The Examiner further asserts that since the prior art recognizes the use of integrin binding partners in the preparation of cells for encapsulation, the ordinary skilled artisan would have had a reasonable expectation of success of substituting the prior art integrin binding partners with a functionally equivalent [emphasis added] integrin binding partner with the expectation of producing similar results, specifically for use in the encapsulation of cells. The Examiner asserts as regards the claims directed to the encapsulation of one cell, that absent evidence to the contrary, since the general parameters of the claimed invention were known in the art, and the claimed invention differs only by the number of cells encapsulated, "variations in the number of encapsulated cells in the prior art method is merely a difference in design choice" [emphasis added]. The Examiner further states "regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions [emphasis added], and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention".

It is respectfully submitted that the inclusion of an integrin binding partner serves several functions in promoting the individual cell's migration from the encapsulation medium and in prolonging the life of the individual cells outside of the encapsulation medium. The influence of the matrix supplementation with integrin binding partners is to enhance cell survival during the transplantation process by avoiding anoikis – i.e., rapid cell death by apoptosis that occurs when cells lose matrix contacts – that would otherwise occur when these attached cells are lifted into a suspension prior to injection. In the context of the beads / capsules of the cited prior art documents, there is no evidence and no teaching that matrix supplementation activates cell survival pathways. Cell growth as Ramdi et al. describe might well result from enhanced proliferation in the presence of cell death. It is therefore unobvious from the cited art that including an integrin binding partner in an encapsulation medium to enhance cell anchorage of very large numbers of cells within large permanent or semi-permanent encapsulation structures, teaches one skilled in the art that the same component could be used in a suspension of individual cells to promote escape from the

encapsulation medium. Therefore, the cited art does not teach or even suggest that individual cells delivered differently (in a suspension) and behaving differently in situ (shedding the encapsulation medium) would interact in functionally the same way with integrin binding partners in an encapsulation medium, when compared to large permanent or semi-permanent encapsulation structures containing very large numbers of cells. Accordingly, it is respectfully submitted that "variations in the number of encapsulated cells in the prior art method is **not** merely a difference in design choice", that one skilled in the art **could not** "have combined the elements as claimed by known methods with no change in their respective functions", and the that such combination would **not** "have yielded predictable results to one of ordinary skill in the art at the time of the invention".

New Claims

The Examiner is referred to the above-referenced passages that discuss the invention in terms of the cells shedding the encapsulation medium. These passages are also relied upon in support of new claims 75 and 82. Claims dependant on claim 75 and 82 closely parallel the language of claims 39 to 41 and 45 to 48.

CONCLUSION

In view of the foregoing comments and amendments to the claims, Applicants believe that claims 38-58, 61-63, 65, and 75-88 are patentable. These are believed to be in condition for allowance.

Allowance of claims 38-58, 61-63, 65, and 75-88 is respectfully requested.

Respectfully submitted,

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